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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/484,542	06/07/95	BRADER	M X-10097

PRICKR EXAMINER

18M1/0909

BANNER & ALLEGRETTI LTD
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WASHINGTON DC 20001-4597

ART UNIT	PAPER NUMBER
1813	4

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

DATE MAILED: 09/09/96

■ This application has been examined ■ Responsive to communication filed on 6/7/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 MONTHS from the date of this letter.
Failure to respond within the time period will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENTS ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ■ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ■ Claims 1-26 are pending in the application.
   Of the above claims, ___ are withdrawn from consideration.
2. ☐ Claims ___ have been cancelled.
3. ☐ Claims ___ are allowed.
4. ■ Claims 1-26 are rejected.
5. ☐ Claims ___ are objected to.
6. ☐ Claims ___ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on ___. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on ___ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on ___ has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under 35 USC 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. ___; filed on ___.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

Status of Claims

1. Claims 12-26 are pending in this Office action.

Claim Rejections

2. Claims 1-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 13 and 16 contain the language "at least about" followed by a concentration range. Does this mean that the lower value of said range is the minimum acceptable concentration but that the upper value is not so limited? Is the range of values variable in some other unexplained fashion? What are the actual limits of concentration considered acceptable given this seemingly ambiguous phraseology?

Claim 25 recites a lyophilized powder "fortified with" zinc. Does "fortified" mean that this zinc present in a bound form with the insulin, or does this term merely reflect the presence of zinc as an added component of the lyophilized powder?

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

4. Claims 1-3, 13 and 14 are rejected under 35 U.S.C. § 102(a) as being anticipated by Havelund et al. [WO 95/07931].

Havelund et al. disclose aqueous fatty acid-acylated insulin formulations containing Zn and a phenolic compound which are identical to the formulations of applicants. On page 56 in Example 29 Havelund et al. disclose N-decanoyl Lys^{B29} human insulin containing Zn and a phenolic compound (i.e., phenol) at pH 7.5 wherein the Zn and phenolic compound are present in amounts or at concentrations which are identical to those recited by applicants. Many insulin analogs prepared in a similar fashion are also disclosed by Havelund et al.. Although the presence of "storage stable" in the preamble is not interpreted as a specific limitation of the claim, the acylated insulin formulations of Havelund et al. would inherently be storage stable.

5. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed. 2nd 545 (1966), 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103 are summarized as follows:

1. Determining the scope and contents of the prior art;
2. Ascertaining the differences between the prior art and the claims at issue; and
3. Resolving the level of ordinary skill in the pertinent art.

7. Claims 1-26 are rejected under 35 U.S.C. § 103 as being unpatentable over Havelund et al. [WO 95/07931] in view of Hashimoto [*Pharm. Res.* **6**, 171-176 (1989)] and Howey et al. [*Diabetes* **43**, 396-402 (1994)].

Havelund et al. disclose aqueous fatty acid-acylated insulin formulations containing Zn and a phenolic compound which are identical to the formulations of applicants. Havelund et al. fail to disclose formulations comprising N-palmitoyl Lys^{B29} human insulin, B28-N^{ε}-(acylated/palmitoyl)-$Lys^{B28}Pro^{B29}$-human insulin, formulations additionally containing normal insulin or an insulin analog, or lyophilized acylated insulin formulations. However, Hashimoto et al. disclose palmitoyl derivatives of insulin including B1,B29-dipalmitoyl-insulin, as a means of improving the absorption characteristics over those of normal insulins. Howey et al. disclose the $Lys^{B28}Pro^{B29}$-human insulin analogue of human insulin having a

reduced capacity for self association. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the palmitoyl derivatives of Hashimoto et al. for the acylated derivatives of Havelund et al., or to acylate the B28-lysine of the analogue of Howey et al. in order to obtain applicant's invention. Motivation to make these alterations of the prior art compounds is provided by the following: 1) Havelund et al. disclose a wide variety of insulin analogs acylated at the B29 Lysine residue. A similar acylated insulin in which the B29 Lys residue is palmitoylated was shown to be biologically active by Hashimoto et al.. Hashimoto et al. also illustrate differences in the time course of action of a B29 Lys palmitoylated insulin derivative versus normal insulin such that the artisan would recognize that inclusion of normal insulin or an analogue thereof along with the acylated insulin would allow greater control of blood glucose levels, 2) Parameters related to concentrations of Zn or phenol, or to the solution pH, are either well known in the art or explicitly defined in the cited prior art such that the choice of these parameters would be obvious to the artisan. Havelund et al., for example, discloses many examples of acylated insulin derivatives in which different Zn/acylated insulin ratios are used. Although the cited prior art references do not specify the Zn salt employed, $ZnCl_2$ and $Zn(OAc)_2$ are the most common forms for biological applications. Havelund also uses various phenolic compounds including cresol and phenol in amounts and at pH values which are identical to those used by applicants, 3) The position of Lysine at B28 in the prior art compound $Lys^{B28}Pro^{B29}$ -human insulin renders obvious the acylation/palmitoylation of this compound at position B28 instead

of position B29 as in the prior art compounds, and 4) lyophilization is routinely used in preparing palmitoyl derivatives of insulin, and this procedure would be recognized as an obvious means of increasing the storage life of acylated insulin derivatives due to the absence of water. For example, the palmitoyl derivatives of Hashimoto et al. are lyophilized before storage prior to preparation of test solutions. Taken together these references would clearly motivate the artisan to obtain the claimed fatty-acid acylated insulin derivatives in order to render obvious applicant's invention.

8. No claims are allowed.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benet Prickril whose telephone number is (703) 305-5933. The examiner normally can be reached Monday through Thursday between 7:30 AM and 5:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703)308-3890. The fax phone number for Art Unit 1813 is (703) 305-7939.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MICHAEL P. WOODWARD
PRIMARY EXAMINER
GROUP 1800